

## REMARKS

### The Invention

Generally, the invention features compositions of isolated neural stem cells that form non-adherent clusters in culture.

### Summary of the Office Action

Claims 32, 33, 41, 42, 49-52, and 54-60 are pending. Claims 32, 33, 49-52, 54-57, 59, and 60 are rejected as being anticipated by Sosnowski et al. (Brain Res. 703: 37-48, 1995) and Ronnett (U.S. Patent No. 5,318,907). All of the pending claims are rejected as being obvious over Sosnowski in view of Anderson et al. (U.S. Patent No. 5,824,489). Each of these rejections is addressed in turn.

### Support for the Amendments

Claims 49-52 have been amended. Support for these amendments is found, for example, at page 16, lines 14-16, and page 20, lines 8-9, of the specification. No new matter has been added.

### Rejections Under 35 U.S.C. § 102

Claims 32, 33, 49-52, 54-57, 59, and 60 are rejected as being anticipated by Sosnowski and Ronnett. According to the Office, Sosnowski and Ronnett each inherently describe compositions containing multipotent neural stem cells. The Office

further states that, because claims 32, 33, 49-52, 54-57, 59, and 60 lack any recitation of purity, these claims are anticipated.

Applicants have amended claims 49-52 (the three independent claims under examination) to clarify that the claimed composition includes isolated neural stem cells. The term “isolated” refers to the fact that cell types other than the stem cells have been removed by killing (see, for example, page 16, lines 14-16, and page 20, lines 8-9, of the specification). The use of the word “isolated” in this respect is consistent with the definition of “isolated” as being “pure; not combined” (Webster’s New Universal Unabridged Dictionary, 2nd Edition).

At no time did the cultures described by Sosnowski or Ronnett consist of isolated stem cells. Sosnowski acknowledges that “[t]he dissociated tissue included mostly olfactory epithelium; however, also included were cells from respiratory epithelium, underlying lamina propria, periosteum and vascular tissue.” (page 38, right column; emphasis added). Ronnett similarly fails to describe isolation of neural stem cells, describing a combination of enzymatic digestion and mechanical dissociation to create cultures of olfactory tissue.

In sum, Sosnowski and Ronnett each fail to describe a population that includes isolated stem cells. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 32, 33, 49-52, and 54-57 as being anticipated.

### Rejections Under 35 U.S.C. § 103(a)

All pending claims (claims 32, 33, 41-47, 49-52, and 54-60) are rejected as being obvious over Sosnowski in view of Anderson. Applicants respectfully traverse this rejection, and maintain their position that (i) there was no motivation to combine the cited references, and (ii) even if there were motivation, the two references do not teach or suggest every element of the claimed invention. These points are addressed in turn.

#### I. There was no motivation to combine the teachings of Sosnowski and Anderson

Even if every element of the claims was taught or suggested by Sosnowski and Anderson (which they are not; see below), there would still be no motivation to combine the teachings of these references. The Office contends that the motivation arises from Anderson's disclosure that nestin-positive stem cells may be derived from the peripheral nervous system, combined with Sosnowski's disclosure that the olfactory epithelium contains multipotent cells. The fallacy with this argument is that not all multipotent cells are nestin positive. As recognized by the Office, Sosnowski did not identify any cultured olfactory cells as being nestin-positive. Anderson, in contrast, describes the isolation of neural crest stem cells having, as one of their hallmarks, nestin immunoreactivity. One skilled in the art would simply not be specifically motivated to look for Anderson's nestin-positive cells in Sosnowski's tissue.

Despite the complete absence of any support in the cited references, the Office continues to assert that the claims are obvious. Applicants note that "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the

applicant's disclosure." *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit recently observed:

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires the Office to show a motivation to combine the references that create the case of obviousness. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). That is, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id.* (emphasis added). In the present case, the Office has not done so. Accordingly, on this basis alone, applicants respectfully request that the rejection of claim 32, 33, 41-47, 49-52, and 54-60 for obviousness be withdrawn.

II. The combination of Sosnowski and Anderson fails to teach or suggest every claim element

The claims as amended include four independent claims: claims 49-52. In each case, the combination of Sosnowski and Anderson fails to teach or suggest every claim element. This is discussed in greater detail below.

Claims 49 and 51

Claim 49 is directed to a composition that includes isolated neural stem cells of a mammal produced by isolating neural stem cells from mammalian peripheral tissue based on their tendency to aggregate and form non-adherent clusters in culture. Claim 51 is directed to a composition that includes isolated neural stem cells that form non-adherent clusters in culture. In each claim, the neural stem cells express nestin, are self-renewing, and are capable of producing dopaminergic neurons.

In order for claims 49 and 51 to be unpatentable over the combination of Sosnowski and Anderson, the two references must together teach or suggest every limitation of the claim. These two references fail to do so for at least two reasons, each of which is discussed below.

First, neither reference teaches or suggests isolating neural stem cells on the basis of their tendency to aggregate and form non-adherent clusters in culture. While the Examiner asserts that the cells of Sosnowski “were isolated...in a fashion similar to the cells claimed in the instant application,” this simply isn’t true. Sosnowski’s cells are produced by enzymatic dissociation of the olfactory epithelium, followed by transfer to

an appropriate culture vessel. Indeed, Sosnowski never produces an isolated composition of neural stem cells by any method; Sosnowski acknowledges that “[t]he dissociated tissue included mostly olfactory epithelium; however, also included were cells from respiratory epithelium, underlying lamina propria, periosteum and vascular tissue.” (page 38, right column; emphasis added). Anderson similarly fails to teach or suggest isolating neural stem cells from peripheral tissue containing sensory receptors on the basis of the cells’ tendency to aggregate and form non-adherent clusters. Anderson’s cells are adherent cells that required treatment with trypsin in order to detach them from the culture surface (see, e.g., column 19, lines 6-8).

The Office maintains that Sosnowski’s cells “would be expected to comprise cells which are capable of forming non-adherent clusters,” despite the clear lack of any teaching in either reference. Applicants respectfully request that the Office indicate the basis for this assertion.

Claims 49 and 51 further require that the claimed stem cells be capable of differentiating into dopaminergic neurons. Neither Sosnowski nor Anderson teaches or suggests that their olfactory cells or neural crest cells, respectively, are capable of differentiating into dopaminergic neurons. Sosnowski, for example, reports only the generation of GABAergic bipolar neurons, and is silent on the ability of the described olfactory cells from differentiating as dopaminergic neurons. Anderson similarly fails to teach or suggest that Anderson’s cells are capable of differentiating as dopaminergic neurons.

The Office asserts that the ability to differentiate as dopaminergic stem cells would be an expected property of multipotent stem cells. Again, the Office reaches this conclusion without any support in the two cited references, and without any evidence. Applicants respectfully request that the Office indicate the basis for this assertion (“If the knowledge is of such notorious character that official notice can be taken, it is sufficient to so state. If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.” M.P.E.P. 2144.03 (citations omitted)).

In sum, Sosnowski and Anderson each fail to teach or suggest at least two limitations of claims 49 and 51. For this reason, applicants respectfully request that the rejection of these claims as being obvious over Sosnowski in view of Anderson be withdrawn.

#### Claim 50

Claim 50 is directed to a composition that includes isolated neural stem cells that (i) form non-adherent clusters in culture, (ii) are self renewing, express nestin and glutamic acid decarboxylase (GAD), (iii) and can differentiate into cell types of the central nervous system.

Again, the combination of Sosnowski and Anderson fails to teach or suggest every limitation. As is discussed above for claims 49 and 51, neither reference suggests that the prior art cells formed non-adherent clusters in culture; only adherent cells are described by these two references. The combination of Sosnowski and Anderson also fails to teach

or suggest the presence of GAD-positive cells, let alone cells that express GAD and nestin.

The Office contends that it multipotent stem cells would be expected to be GAD-positive, but provides no support for this; such support is respectfully requested.

As neither Sosnowski nor Anderson even suggests these claim elements, it follows that no combination of these two references can result in the claimed composition of claim 50. Applicants request that this rejection be withdrawn.

#### Claim 52

The fourth independent claim, claim 52, is directed to a composition includes a isolated neural stem cells that form non-adherent clusters in culture, are self renewing, proliferate in an EGF-independent manner, and can differentiate into cell types of the central nervous system. Like the preceding three independent claims, claim 52 thus requires the presence of cells that form non-adherent clusters in culture. As is discussed above, the two references relied upon by the Office fail to describe such non-adherent cells. Sosnowski and Anderson also fail to describe another feature of the cells of claim 52: the ability to proliferate in an EGF-independent manner. Sosnowski and Anderson each culture their respective cells in the presence of EGF. In the case of Sosnowski, the EGF is provided as a component of fetal bovine serum (page 38, right column); Anderson adds recombinant EGF (column 15, lines 9-10). As neither Sosnowski nor Anderson teach or suggest at least two elements of the claim, the rejection of claim 52 as being obvious over Sosnowski in view of Anderson should be withdrawn.



### Dependent claims

The remaining claims (claims 32, 33, 41-47, 49-52, and 54-58) depend from one or more of the four independent claims discussed above. As the independent claims are non-obvious over the cited references, it follows that the dependent claims are non-obvious as well.

### Conclusion

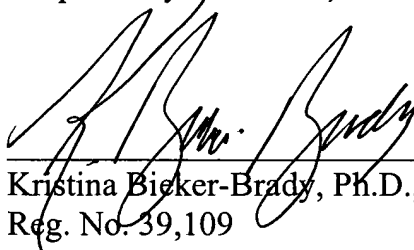
Applicants hereby submit that the claims are now in condition for allowance, and such action is respectfully requested. If the claims are not deemed to be in condition for allowance, the undersigned requests a telephone interview in order to discuss the remaining rejections.

Enclosed is a petition to extend the period for replying to the Office Action for three months, to and including February 26, 2004, and a check in payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date:

February 26, 2004



Kristina Bieker-Brady, Ph.D., P.C.  
Reg. No. 39,109

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045